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REVIEW



# Current and emerging medical therapeutic agents for idiopathic male infertility

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**ABSTRACT**

**Introduction**: Infertility is one of the great challenges of modern healthcare. It afflicts about 8–12% of reproductive-aged couples worldwide, but the prevalence is even higher in industrialized countries. In 50% of cases, a male factor of infertility underlies the problem, but in about 30% of these cases the etiology of male infertility remains unknown. This eventuality, called idiopathic infertility, requires empirical medical therapy and/or assisted reproductive techniques.

**Areas covered**: This article reviews the literature about the medical treatments available for idiopathic male infertility. These treatments can be divided into two main categories: hormonal therapies and non-hormonal therapies. The compounds with the strongest evidence of efficacy and the most used in clinical practice for the treatment of idiopathic male infertility are follicle-stimulating hormone (FSH) and estrogen receptor selective modulators (SERMs). Non-hormonal treatments include a series of compounds with antioxidant and prokinetic properties, supported by variable degrees of evidence of clinical efficacy.

**Expert opinion**: Patients with idiopathic infertility have peculiar clinical features that differentiate them from each other. Therapy must, therefore, be personalized to each patient. Furthermore, scientific research must investigate the pathophysiological mechanisms that underlie infertility; only in this way, new targeted therapies can be developed.

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Idiopathic male infertility; empiric treatment; medical therapy; azoospermia; oligozoospermia; oligoasthenoteratozoospermia; FSH; hCG; aromatase inhibitors; SERMs

## 1. Introduction

Infertility is defined as the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse, due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner [1].

Infertility affects about 8–12% of reproductive-aged couples worldwide [2]. Male factor is responsible for about 50% of cases of infertility overall: alone (~ 30%) or in association with a female factor of infertility (~ 20%) [2]. Despite a complete diagnostic workup, in approximately 30% of cases of male infertility no obvious cause for abnormal sperm parameters can be found [3]. This occurrence is defined 'idiopathic infertility' [4]. Male patients affected by idiopathic infertility are usually treated with an empiric medical therapy or addressed to medically assisted reproduction techniques (ART) [5].

The purpose of this review was to summarize the most recent evidences about the efficacy of the main compounds (hormonal and non-hormonal) used in the empirical treatment of male idiopathic infertility.

## 2. Hormonal therapies

### 2.1. Gonadotropins

Starting from the 50s, therapy with gonadotropins and gonadotropin-releasing hormone (GnRH) analogues was tested in patients with idiopathic infertility in the attempt to improve sperm parameters and the pregnancy rate [6].

The use of GnRH was progressively abandoned for its uncomfortable route of administration. Until the end of the 70s, human chorionic gonadotropin (HCG), alone [7] or in combination with human menopausal gonadotropin (hMG) [8], was employed in the treatment of male infertility.

In the mid-80s, urofollitropin—an hormone with FSH-like activity extracted from the urine of menopausal women—became available and it began to be empirically used in the treatment of oligoasthenozoospermia [9].

Pure FSH was obtained in the second half of the 90s [10], while the recombinant FSH in the 2000s [11]. Recently, formulations of biosimilar FSH have been marketed [12].

Recombinant luteinizing hormone (LH) is also available, but it is not used in clinical practice because of its short half-life (~ 10 h) [13].

Nowadays, gonadotropins are the treatment of choice in male infertility due to hypogonadotropic hypogonadism (hypothalamic or hypophyseal). However, over the years, their effectiveness in the treatment of idiopathic male infertility has also been investigated.

#### 2.1.1. Follicle-stimulating hormone (FSH)

FSH is a hormone produced by the anterior pituitary gland which, together with LH, regulates the gonadal activity in both men and women. In the testis, FSH activates the proliferation of the Sertoli cells, induces the mitosis of the spermatogonia and supports cellular differentiation up to the round spermatid stage [14]. Furthermore, FSH together with testosterone seems to promote

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**Article highlights**

- A male factor is responsible in about 50% of cases of couple infertility. In 30% of cases, the cause of male infertility remains unknown, despite an accurate diagnostic work up
- The treatment of idiopathic male infertility consists in the application of ART or empirical medical therapy, which may be hormonal or non-hormonal
- Among the hormonal therapies the most effective are SERMs and FSH; among non-hormonal therapy the strongest evidences of effectiveness are about carnitines, coenzyme Q10, myoinositol, some vitamins and trace elements
- It would seem that the association between hormonal and non-hormonal therapy is more effective than using one or the other; but, in all cases, the therapy must be personalized for each patient
- Scientific research must engage in further clarifying the pathophysiology of infertility to reduce the number of cases still considered idiopathic. An emerging research field could be the interaction between intestinal microbiota and reproductive function
- Clinicians must always carry out a careful diagnostic work-up to identify any factors that may hinder conception (including seminal rheological alterations and unrecognized infections), before starting an empiric therapy for infertility

This box summarizes key points contained in the article.

spermiogenesis by regulating the adhesion of round spermatids to Sertoli cells [15]. In fact, it has been demonstrated that contemporary FSH and testosterone and suppression causes spermiation failure because of a dysfunction in the final disengagement of spermatids from the Sertoli cell [16].

As gonadotropins represent an effective treatment in hypogonadotropic hypogonadism [17], the therapy with human FSH has been experimented also in patients with idiopathic infertility and normal plasma concentrations of gonadotropins, in an attempt to improve sperm concentration, spermatogonial population, and the pregnancy rate. The therapy has been approved for male patients with idiopathic infertility, but, in this category of patients, the results seem to be still controversial: some authors reported improvement in sperm parameters and/or in the pregnancy rate after FSH administration, while other authors showed no benefits [18].

Recently, two meta-analysis have been published. In 2013, a Cochrane review including only randomized controlled trials (RCTs) showed a significant increase in spontaneous pregnancy rate in infertile patients who received FSH (16%) vs. placebo or no treatment (7%) [19]. In 2017, Santi and colleagues included all available controlled clinical trials and showed a significant increase in sperm concentration and in spontaneous and post-ART pregnancy rates [20].

More recently, some other studies have confirmed the effectiveness of FSH in improving sperm parameters and/or pregnancy rates in normogonadotropic oligozoospermic infertile patients [21,22]. Furthermore, therapy with FSH before ART has proven to be effective in increasing pregnancy rate and fertilization rate in patients with sperm maturation arrest [23] and in azoospermic patients who underwent testicular sperm extraction (TESE) [24]. In the latter case, although the patients who were treated remained azoospermic, FSH seems to increase the retrieval rates by TESE [24], but further studies are needed.

Some studies have also reported a decreased sperm DNA fragmentation rate in patients treated with FSH [21,25,26], suggesting that this therapy may improve sperm quality as well as sperm concentration.

FSH formulations available today on the market are extracted and purified from the urine of postmenopausal women [purified or high-purified FSH (hpFSH)], obtained from DNA recombinant technology (rhFSH) [27], or biosimilar FSH [12].

The lowest dose of FSH and the minimum duration of therapy useful for improving sperm parameters have not yet been clearly established. They seem to depend on the type of FSH used [18]. The posology of hpFSH most frequently used and that has shown some effectiveness in increasing sperm concentration and motility is 150 IU or 75 IU on alternate days for three months, while for rhFSH the effective dosage seems to be higher (˃450 IU/week) [18]. Recently, Ding and collaborators showed that sperm count increases significantly with a dose of at least 200 IU of rhFSH on alternate days and that the improvement is observed starting from the third month of therapy [28]. Better results seem to be obtained with doses of rhFSH of 300 IU administered on alternate days for five months [28].

In general, although most of the studies report data after 3 months of therapy, it seems that the efficacy increases after longer time of administration, and this finding is coherent with the knowledge that the process of spematogenesis lasts about 72 days [18].

Instead, there are no clinical trials to date on the use of biosimilar FSH for the treatment of idiopathic male infertility. Recently, Mastrangelo and colleagues studied the in vivo biological activity and glycosylation of biosimilar vs. rhFSH. They showed differences between the two formulations in the glycosylation profile at the Asn52 site of the α-chain: biosimilar FSH showed higher antennarity, higher sialylation and higher batch-to-batch variability in activity compared with rhFSH. The clinical relevance of these differences should be still investigated [29].

FSH therapy is ineffective in patients with high values of endogenous gonadotropins. However, not all patients with normal gonadotropin values obtain an increase in sperm concentration after FSH administration [30]. It is known that some polymorphisms of the FSHR gene may determine interindividual variability in quantitative expression and receptor sensitivity, affecting the response to FSH [26]. The most studied polymorphism is the A⁄G transitions at nucleotides 919 and 2039 of exon 10 that causes the replacement of threonine with alanine in position 307 and of asparagine with serine in position 680 of the polypeptide transcript (Ala307Thr-Asn680Ser) [31]. This gives rise to two allelic variants—Thr307-Asn680 (TN) and Ala307-Ser680 (AS)—and three different possible genotypes: TN/TN, TN/AS and AS/AS [31]. It has been showed that only men with at least one serine in position 680 (genotypes TN/AS and AS/AS) respond to FSH administration [32]. Therefore, the research of this polymorphism could be useful in selecting patients candidates for FSH treatment and to explain some cases of non-response to therapy.

Another important polymorphism is present on the promoter of the FSHB gene, in position −211: in this site, a single-nucleotide polymorphism (SNP) G/T, leading to three genotypes (TT, GG e GT), seems to be responsible for the endogenous FSH levels [33]. Indeed, Ferlin and collaborators showed that patients with FSHB − 211 TT genotype have lower endogenous FSH levels and better responses to FSH treatment in term of increase in sperm count compared to GG and GT genotypes [34]. Similarly to the previous one, FSHB—211 polymorphism can also be helpful in selecting patients who could benefit from FSH therapy.

Another predictor of response to FSH administration could be represented by serum inhibin B levels. Inhibin B concentration correlate positively with testicular volume and sperm concentration, and negatively with FSH serum levels [35]. When spermatogenesis is dysregulated, inhibin B levels decrease and FSH levels increase. Thus, the level of inhibin B is a useful marker of testicular damage, and both inhibin B and FSH serum levels should be within the normal range for a greater likelihood of success to exogenous FSH administration [30].

### 2.1.2. Human Chorionic Gonadotropin (HCG)

Adequate intratubular testosterone (T) concentrations are essential for the spermatogenesis (Figure 1) [36]. T induces Sertoli cell maturation, resulting in downregulation of AMH expression and in triggering germ cells meiosis [36].

hCG exerts LH-like effect, leading to an increase in T concentration more pronounced at the intratesticular level than in peripheral blood [37]. hCG is, today, used in men with hypogonadotropic hypogonadism and demand for fertility in association with FSH. In fact, in these patients, FSH alone is ineffective in initiating and/or maintaining spermatogenesis because of the intratesticular testosterone deficiency [38]. On the contrary, the administration of hCG alone proved to be effective in restoring intratesticular T concentrations and inducing spermatogenesis [39]. The therapy with hCG is also effective in improving T levels preserving fertility in patients with late-onset hypogonadism and desire of fatherhood [40]. Finally, hCG therapy has been recently used to preserve spermatogenesis in men undergoing T replacement therapy [41,42]. In fact, exogenous T administration causes LH suppression, and, consequently, the Leydig cells steroidogenic activity shutdown. Low doses of hCG could prevent the downfall of intratesticular T levels [38].

In patients with idiopathic infertility data are less encouraging. Few studies used hCG alone [7,43]. Most of the studies were performed in the 80s, using hCG in association with hMG [8,44–47]. The latter contains also a variable amount of FSH; therefore, in these studies, it is not possible to distinguish which of the two drugs is responsible for the effects obtained. Anyway, most of these studies showed an improvement in sperm parameters and pregnancy rate [8,44,45,47].

## 2.2. Aromatase Inhibitors (AIS)

In men, the main estrogens are 17β-estradiol ($E_2$) and estrone. They, respectively, derive from the conversion of T and androstenedione catalyzed by aromatase, a cytochrome P450 enzyme present in many tissues and organs such as testis, adipose tissue, liver, and brain [48]. AIs are drugs that block

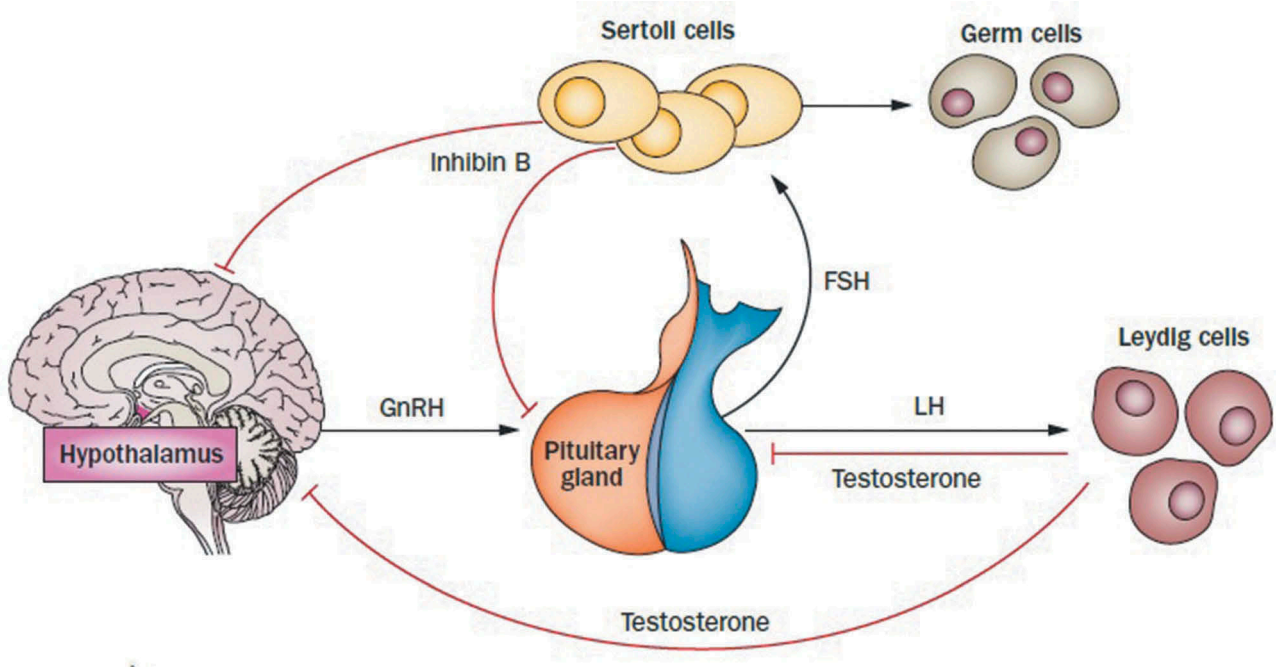


Figure 1. Spermatogenesis in men (Reproduced from Valenti et al., 2013 [30] with permission of Springer Nature).Spermatogenesis depends on the pulsatility of GnRH secretion and this, in turn, induces the pulsatile release of the gonadotropins LH and FSH by the pituitary gland. Both LH (indirectly via T production) and FSH (acting on Sertoli cells) stimulate spermatogenesis. FSH increases the expression of the androgen receptor, rendering Sertoli cells more-responsive to T. T is secreted by Leydig cells, which feeds back on pituitary LH-secreting cells to inhibit their function. Similarly, inhibin B—predominantly released by Sertoli cells—inhibits FSH secretion.

the aromatase activity and thus the conversion of androgens into estrogens. The compounds most used in clinical practice are non-steroidal molecules, which cause reversible enzyme inhibition, such as letrozole and anastrozole. They have been used in idiopathic male infertility in the attempt to reduce the negative feedback exerted by estrogens on the hypothalamic–pituitary–gonadal axis, to improve LH secretion and, consequently, enhance intratesticular testosterone levels and spermatogenesis [49].

Based on the observation that a low T/E2 ratio was associated with infertility in men, Pavlovich and colleagues proposed a cut-off value of 10, below which the $T/E_2$ ratio has to be considered pathologic [50].

In patient with $T/E_2$ ratio below 10, AIs proved to be effective in improving sperm parameters, serum T levels, and spontaneous pregnancy rate, as well as in restoring spermatogenesis in some azoospermic patients [48,51–53]. Most of the patients enrolled in these studies had moderately low total T concentrations and high body mass index (BMI) values. Aromatase is an enzyme highly represented in adipose tissue, and this explains why overweight/obese patients show averagely higher values of $E_2$, lower $T/E_2$ and a better response to AIs.

Although they have proven their effectiveness in some categories of patients, a recent systematic review showed the low quality of the studies regarding the effectiveness of AIs therapy in infertile men [54]. Therefore, further randomized trials are needed.

### 2.3. Selective Estrogen Receptor Modulators (SERMs)

Similarly to AIs, SERMs act blocking the negative feedback exerted at the hypothalamus-pituitary level by estrogens. The reduction of the negative feedback causes an increase in the secretion of GnRH and gonadotropins [55]. Speculatively, the rise of LH would stimulate Leydig cells, leading to an increase in T concentration; while the increase in FSH would lead to an improvement in spermatogenesis acting on Sertoli cells [56]. For this reason, the treatment results ineffective in infertile patients with elevated levels of endogenous gonadotropins (primary hypogonadism) or in men with altered hypothalamic-pituitary axis (congenital or acquired hypogonadotropic hypogonadism) [55].

The most studied and mainly used compounds of this pharmacological class are clomiphene and tamoxifen. According to an American survey, clomiphene is also the most used drug in empirical medical management of idiopathic male infertility, at least in the United States [57]. Estrogen antagonists are relatively safe drugs although, compared to AIs, they have the disadvantage of increasing estrogen production in addition to testosterone [58]. The potential side effects of clomiphene and tamoxifen include nausea, hot flushes, headache, visual disturbances and cardiovascular disorders, but they have a low incidence and are usually transient [59].

Several evidences showed the effectiveness of these drugs in moderately increasing sperm concentration, but data on the spontaneous pregnancy rate are controversial. In particular, three meta-analysis grouped the results of clinical trials conducted on patients with idiopathic oligoasthenozoospermia treated with SERMs. The first one was conducted in 1999 and concluded for a non-significant higher pregnancy outcome among patients treated with estrogen antagonists vs. controls [60]. The second one was a Cochraine review, published in 2000 and withdrawn in 2007, that included 10 studies involving 738 patients treated with clomiphene or tamoxifen. Authors concluded that anti-estrogens had a positive effect on endocrine outcomes, such as serum T levels, but no significant difference was found in the pregnancy rate between treated patients and the control groups [61]. The last meta-analysis was conducted in 2013 and included eleven RCTs of good methodological quality. Data analysis showed that estrogen antagonists induce a significant elevation of serum FSH and T levels, sperm concentration, per cent sperm motility and pregnancy rate compared with controls [62]. In particular, the chance of pregnancy was 2.4 times greater among patients with idiopathic infertility treated with estrogen antagonist vs. control group. Finally, this review points out that 50 mg of clomiphene and 20–30 mg of tamoxifen are the effective daily dose for the treatment with estrogen antagonists, which must last from 3 to 6 months, without reaching 12 months [62].

Some studies showed that SERMs are more effective when given in combination with antioxidant compounds (i.e. vitamin E) [63–65]. Guo and colleagues recently demonstrated that tamoxifen itself has antioxidant properties: its administration significantly increased sperm mitochondrial functionality and, subsequently, increased sperm motility by reducing oxidative stress [66].

In two studies, clomiphene and tamoxifen also showed their effectiveness in recovering spermatozoa in the ejaculate of some azoospermic patients with hypospermatogenesis or maturative arrest, and in increasing sperm retrieval by TESE [67,68].

## 3. Non-hormonal therapies

### 3.1. Antioxidant and prokinetic compounds

One of the factors that may contribute to the onset of male infertility is the overproduction of reactive oxygen species (ROS) [69]. The presence of a low amount of free radicals is essential for the spermatogenetic process [70]. ROS generated by NADPH oxidase 1 are implicated in the self-renewal of spermatogonial stem cells and contribute to germline stem cell proliferation [71]. Other processes requiring higher threshold of ROS are sperm hyperactivation, capacitation, and acrosome reaction during fertilization [70]. However, supraphysiological ROS levels have detrimental effects on sperm function, being able to cause lipid peroxidation, sperm DNA damage, and abortive apoptosis, and to alter conventional sperm parameters such as motility [72–74]. About 20–40% of infertile patients have high seminal ROS concentrations, that represent an independent marker of male infertility, irrespective of sperm parameters alterations [75].

Conditions that increase the oxidative stress on spermatozoa above the physiological levels include diseases of the

reproductive tract (i.e. varicocele, male accessory gland infection/inflammation), unhealthy lifestyles (i.e. cigarette smoking, alcohol abuse, drug addiction), environmental pollution (i.e. radiation, smog, industrial gasses) and food misconduct (i.e. hyperlipidic diet) [76]. Spermatozoa are more susceptible than other cell types to the harmful effects of ROS because their plasma membrane, containing high amount of polyunsaturated fatty acids, is very sensitive to lipid peroxidation [76]. Furthermore, the process of sperm chromatin condensation is very susceptible to increased oxidative stress because spermatozoa have low levels of cytoplasmic antioxidant enzymes and inefficient DNA repair mechanisms [70].

ROS have been shown to alter motility, morphology and sperm DNA stability [73]. Their concentration in spermatozoa can be assessed through the evaluation of sperm oxidized DNA (8-hydroxy-2′–deoxyguanosine (8OH-2DG)) and/or the measurement of seminal levels of malondialdehyde, a marker of lipid peroxidation [77].

Mitochondrial membrane potential (MMP) is the parameter that best reflects mitochondrial function. It is an important indicator of mitochondrial energy status: high MMP values are associated with better sperm motility, while low values are associated with a decreased sperm motility [78]. In fact, MMP and ROS levels are inversely correlated: ROS damage the mitochondrial membrane and the damaged mitochondrial, in turn, produces a higher amount of ROS, creating a vicious circle [79].

Another important parameter that is affected by ROS overproduction is the integrity of the sperm DNA, that can be assessed by different laboratory tests (i.e. Comet assay, TUNEL assay, sperm chromatin structure assay, sperm chromatin dispersion) [80]. Couples with low sperm DNA fragmentation levels have 2.5 times higher live birth rate than couples with high sperm DNA fragmentation levels, and 39% of couples with idiopathic infertility have high sperm DNA damage [81,82].

Starting from these assumptions, the nutritional supplementation with antioxidants has been developed in the attempt to improve sperm quality in patients with idiopathic infertility. Antioxidant substances include a long list of enzymatic factors, non-enzymatic molecules and low molecular weight compounds [77,83]. However, some of these compounds are not used in clinical practice because they have uncomfortable administration routes (e.g. intramuscular) or because they lack of effectiveness in improving sperm parameters and pregnancy rate [77,83].

In 2011, Gharagozloo and Aitken reviewed 20 studies conducted on infertile male patients treated with antioxidant. The data analysis showed a significant decrease in oxidative stress indices on semen and improved motility in asthenozoospermic patients. Half of the studies reported pregnancy-related outcomes, and most of them revealed positive associations between antioxidant therapy and pregnancy rate [84].

All antioxidant compounds have a prokinetic activity, mainly due to their ability to reduce ROS concentrations, to improve mitochondrial function and, in turn, to enhance sperm motility. However, some molecules play a prokinetic role also with other mechanisms. For example, carnitines enhance sperm motility by improving intramitochondrial fatty acid transport [85], while myoinositol, a phosphatidylinositol precursor, acts with a post-receptor mechanism [76].

The properties of the main antioxidant and prokinetic compounds used in the clinical practice are summarized below and in Table 1. The other antioxidant substances are listed in Table 2.

Table 1. Mechanism of action, daily dosage, effect on sperm parameters and pregnancy rate of the main commercially available antioxidant and prokinetic compounds.

| SUBSTANCE | PROPOSED MECHANISMS OF ACTION | EFFECT ON SPERM PARAMETERS | | EFFECT ON PREGNANCY RATE | DAILY DOSE | REFERENCES |
|---|---|---|---|---|---|---|
| Carnitines | • Antioxidant activity<br>• Fatty acids carriage<br>• Antiapoptotic effect<br>• Protection from heat-induced damage | Count<br>Motility<br>Morphology | ↑<br>↑<br>↑- | ↑- | 3000–4000 mg | 94–99 |
| Coenzyme Q10 | • Antioxidant activity<br>• Mitochondrial electron transport | Count<br>Motility<br>Morphology | ↑-<br>↑<br>↑- | ↑- | 200–300 mg | 103–107 |
| Myoinositol | • Antioxidant activity<br>• Effect on cell morphogenesis and cytogenesis<br>• Osmotic regulation<br>• Stimulation of capacitation and acrosome reaction | Count<br>Motility<br>Morphology | ↑<br>↑<br>↑- | - | 2000–4000 mg | 117–120 |
| Vitamin C | • Antioxidant activity | Count<br>Motility<br>Morphology | -↑-<br>↑-<br> | - | 200–1000 mg | 122,131,132,135 |
| Vitamin E | • Antioxidant activity | Count<br>Motility<br>Morphology | ↑-<br>↑<br>↑- | ↑- | 100–1200 mg | 128–130,132–136 |
| Lycopene | • Antioxidant activity | Count<br>Motility<br>Morphology | ↑-<br>↑<br>↑- | ↑- | 4–30 mg | 139–141 |
| Selenium | • Antioxidant activity<br>• Enzyme cofactor | Count<br>Motility<br>Morphology | ↑-<br>↑<br>↑- | - | 100–225 µg | 134,147,148,150 |
| Zinc | • Antioxidant activity<br>• Enzyme cofactor | Count<br>Motility<br>Morphology | ↑-<br>↑<br>↑ | ↑- | 66–500 mg | 151–156 |

Legenda: '↑' three or more studies showing improvement; '↑-' two or less studies showing improvement or conflicting data; '-' no evidence of improvement

Table 2. Other antioxidants.

| Enzymes | Superoxide dismutase, catalase, glutathione peroxidase |
|---|---|
| Polypeptides and amino acids | Glutathione, N-acetyl-cysteine, arginine, taurine, ornithine, citrulline |
| Vitamins | Vitamins of group B complex, niacin (vitamin PP), pantothenic acid, folic acid |
| Trace elements | Magnesium, copper |
| Omega-3 fatty acids | Docosanoic acid (DHA), eicosanoid acid (EPA) |
| Phytoextracts | *Haematococcus pluvialis* (astaxanthin), *Serenoa repens, Curcuma longa, Camellia sinensis, Urtica dioica, Lepidium meyenii Walp., Muira puama, Ginkgo biloba, Scutellaria baicalensis, Georgi radix, Pinus massoniana, Cucurbita maxima, Aesculus hippocastanum, Crocus sativus, Epilobium (angustifolium and parviflorum), Citrus bergamia, Orthosiphon*, etc. |

### 3.1.1. Carnitines

Carnitine is a carboxylic acid and short chain amino acid, belonging to the methylamine family. It is a carrier that conveys fatty acids inside the mitochondria to be used for the ATP production. In humans, carnitine is present in two main forms: L-carnitine and L-acetylcarnitine [85]. L-carnitine has also antiapoptotic effects, due to the ability to inhibit programmed cell death mediated by FAS-FAS ligand and caspase 3, 7, and 8 [86].

Carnitine is present in high concentrations in the male reproductive tract, and particularly in the epididymis, enough to be considered a marker of epididymal function [87]. In fact, decreased L-carnitine concentration have been found in the seminal fluid of patients with epididymitis [87], and its supplementation after the eradication of the pathogenic noxa (bacterial or inflammatory) has been proven capable of improving sperm parameters [88–90].

At testicular level, L-carnitine also showed protective effect from heat-induced damage and, consequently, the ability to decrease germ cell apoptosis rate [86].

Carnitine is thought to be involved in the regulation of sperm maturation and sperm motility, and this hypothesis would seem confirmed by the observation that in vitro incubation with carnitine leads to an increase in sperm motility [91]. Furthermore, in patients with asthenozoospermia, a lower seminal concentration of carnitine has been observed compared to controls [92].

Despite a randomized, double-blind, placebo-controlled trial failed to show clinically or statistically significant effect of carnitine supplementation on sperm motility [93], carnitine is probably the antioxidant with the most proven efficacy in the literature. In fact, several studies have shown the beneficial effects of in vivo treatment with L-carnitine and/or L-acetylcarnitine on sperm parameters and pregnancy rate of patients with idiopathic asthenozoospermia [94–99]. The daily dosage administered in these studies was 3 g of L-carnitine or L-acetylcarnitine when used severely [95,96,99]; 2 g of L-carnitine plus 1 g of L-acetylcarnitine when administered in combination with each other [97–99]. Only one study used 4 g/d of L-acetylcarnitine [94]

### 3.1.2. Coenzyme $Q_{10}$

Coenzyme $Q_{10}$ (CoQ10) is an endogenous lipid-soluble antioxidant that regulates the mitochondrial electron transport in the respiratory chain and the permeability of outer mitochondrial membrane [100]. CoQ10 also protects against oxidative stress thanks to its ability to inhibit hyperoxide formation, as shown by the correlation between CoQ10 concentration and $H_2O_2$ levels [101].

In an in vitro study, the incubation with CoQ10, zinc and D-aspartic acid lowered sperm lipid peroxidation in both normozoospermic men and asthenozoosepermic patients, and improved significantly sperm motility in the latter. This resulted in a significantly higher number of spermatozoa with progressive motility recovered after swim-up in both group [102].

In vivo, it has been shown that the CoQ10 oral administration in patients with idiopathic oligoasthenoteratozoospermia (OAT) improves sperm parameters (concentration, motility, and morphology) [103–105] and pregnancy rate [106]. Another study failed to show significant changes in sperm parameters of patients with idiopathic OAT treated with CoQ10, even if total antioxidant capacity of seminal plasma significantly increased [107].

A meta-analysis of three controlled randomized trials confirmed a statistically significant increase in sperm concentration and motility, but failed to demonstrate an improvement in sperm morphology and pregnancy rate [108].

The CoQ10 dose administered in the above mentioned studies was 200 mg [103,105,107] or 300 mg [104,106] daily.

### 3.1.3. Myoinositol

Myoinositol is a component of the vitamin B complex and a precursor of the phosphatidylinositol polyphosphates, molecules involved in the intracellular signal transduction [76]. As well as having antioxidant properties, myoinositol participates in cell morphogenesis and cytogenesis, particularly in the formation of cell membranes, lipid synthesis and cell growth [77]. It has osmotic properties and it could contribute to seminal fluid volume regulation [109]. It also seems to control motility, chemotaxis and thermotaxis of human spermatozoa. Sperm thermotaxis is a fundamental process for fertilization because it stimulates the migration of spermatozoa from colder to warmer areas (such as oviducts at the time of ovulation) [110]. Migration is guaranteed by the flagellum that acquires motility thanks to the binding of inositol 1,4,5-triphosphate to its receptors and to the subsequent entry of calcium ions [110]. Inositol triphosphate receptors have also been found in the cytoplasmic membrane, mitochondria, head and neck of the spermatozoa, and in the sperm acrosome of mice and dogs, suggesting a role for myoinositol in the process of capacitation and subsequent acrosome reaction [111]. In particular, in the sperm head, inositol triphosphate receptors favor the entry of calcium that modulates the activity of different enzymes (phospholipase C, protein kinase C, phospholipase A2) involved in the sperm binding to the zona pellucida and the exocytosis of the acrosome content [112].

It has been demonstrated that the in vitro incubation of sperm with myoinositol enhances MMP and sperm motility [113,114], and increases the number of spermatozoa recovered by swim-up [115]. Furthermore, in a recent study, sperm pretreatment with myoinositol improved the fertilization rate in ICSI cycles [116].

Regarding the in vivo effects, the oral myoinositol administration proved to be safe and effective in improving seminal parameters [117–120], even if a single study failed to demonstrate an increase in sperm motility [118]. Myoinositol administration also led to an improvement in serum gonadotropin, inhibin B and testosterone levels [117,119]. However, data on pregnancy rate are not available. So, further investigations are needed.

The myoinisitol dosage most used in the above mentioned studies was 2000 mg daily [117,119,120].

### 3.1.4. Vitamins C and E

Vitamin C (ascorbic acid) is a water-soluble, weakly acidic compound with the ability to neutralize hydroxyl, superoxide, and hydrogen peroxide radicals. Vitamin E (α-tocopherol) is a fat-soluble compound, capable of preventing the peroxidation of membrane phospholipids through the neutralization of free hydroxyl radicals and superoxide anions [121]. It has been shown that the seminal concentrations of both these vitamins are significantly related to the percentage of motile spermatozoa [122,123], and they are lower in patients with altered sperm parameters than in normozoospermic men [124]. Furthermore, vitamin C levels correlate positively with the percentage of morphologically normal spermatozoa [125] and negatively with sperm DNA fragmentation index [126].

In vitro, Baker and colleagues tested the ability of some antioxidant compound to decrease the loss of sperm motility caused by ROS generated by polymorphonuclear leukocytes. They showed no significant protective effects of the combination of vitamin C and E on the sperm damage caused by activated granulocytes [127].

While the in vivo studies that investigate the effectiveness of the treatments with one vitamin alone are few [122,128–131], the studies on the association between the two vitamins or between a vitamin and other antioxidants are more consistent [132–136]. Most of the studies showed decreased seminal ROS levels, improved sperm parameters, and/or increased pregnancy rate [130,131,133,134,136]. In contrast with these findings, Rolf and colleagues, in a randomized, placebo-controlled, double-blind study, observed no changes in sperm parameters and no pregnancies during oral administration of vitamins C and E, but they used very high dosage of both vitamins (1000 and 800 mg daily, respectively) [132]. Another study with high dosage of vitamin C and E did not show improvement in conventional sperm parameters but reported a decrease in sperm DNA fragmentation [135].

The daily dose used in these studies ranged from 200 to 1000 mg for vitamin C and from 100 to 1200 mg for vitamin E. Interestingly, the highest doses proved to be less effective in enhancing sperm parameters [132,135], maybe because of an hormetic effect.

### 3.1.5. Carotenoids

Carotenoids are natural antioxidant substances contained in yellow, red, orange, and pink vegetables. Their deficiency in the diet has been related to decreased sperm motility [121].

Vitamin A, also known as retinol, derives from carotenoids. It regulates epithelial cell proliferation, and some steps of spermatogenesis [77]. It has been shown that men with lower serum concentration of retinol have worse sperm quality [121]. Despite no randomized studies evaluated the effects of oral supplementation with vitamin A on human sperm parameters, it is currently present in lots of preparation for the treatment of male infertility.

Lycopene is a carotenoid contained in fruits and vegetables that belongs to the human redox defense system for its ability to neutralize singlet oxygen [137]. It has been demonstrated that the addition of lycopene to cryoprotectant during cryopreservation prevents sperm mitochondria oxidative damage, attenuates oxidative stress injury induced by ROS to sperm plasma membrane, and improves the anti-apoptotic sperm ability [138]. For these in vitro properties, oral supplementation with lycopene has been attempted in vivo to enhance sperm parameters. Although few studies investigated its effects, lycopene oral administration seems to improve sperm concentration, motility, and morphology [139–141]. Mohanty and collegues also showed an increase in pregnancy rate, but the study was neither randomized nor placebo-controlled [139].

The data seem promising but further studies are needed.

The lycopene dosage used in these studies ranged from 4 to 30 mg daily.

### 3.1.6. Trace elements

Selenium is a micronutrient involved in testicular development, spermatogenesis, and sperm function. It is an essential component of selenoproteins, including some enzymes involved in defense against oxidative stress, such as glutathione peroxidase [142]. Its lack has been correlated to seminiferous epithelium atrophy and testis volume decrease, defects of spermatogenesis and sperm maturation, and altered sperm motility and morphology [121,143,144].

Like selenium, zinc is a component of numerous enzymes involved in the defense against oxidative stress (i.e. superoxide dismutase), in DNA repair and transcription, and in cell replication [121]. It has been shown that patients with idiopathic infertility have lower seminal zinc concentrations than fertile men [145].

These trace elements are contained in numerous commercial products for male infertility but few clinical trials have evaluated singly their effectiveness.

In vitro, the sperm incubation with selenium increased sperm MMP and motility, and decreased sperm DNA fragmentation and malondialdehyde levels [146]. In vivo the data are conflicting. In a double-blind, placebo controlled, randomized study all sperm parameters significantly improved after 26 weeks of daily oral selenium administration [147]. On the contrary, in two other studies, the selenium supplementation showed no effect on sperm parameters [148,149]. Improvement of sperm concentration, motility and morphology has also been reported with the administration of selenium in combination with N-acetylcysteine and vitamin E [134,136,150]. In these studies, the selenium administered dose was 100–225 μg/d.

In vivo, oral zinc supplementation proved to be effective in reducing markers of oxidative stress and in enhancing sperm concentration, motility, and/or morphology in asthenozoospermic and infertile patients [151–155]. Omu and colleagues also reported a decrease in sperm DNA fragmentation after 3 months of oral zinc administration [153]. Furthermore, two study reported an increase in pregnancy rate [151,152]. On the contrary, a placebo controlled study did not report any improvement in sperm parameters after 16 weeks of zinc oral supplementation [156].

The zinc sulfate daily dose administered in these studies ranged from 66 to 500 mg.

### 3.2. Probiotics and prebiotics

In recent years, it has been discovered that the gut microbiota has pleiotropic physiological effects. In facts, it would seem to regulate not only the intestinal function but also the immune system, the organ morphogenesis, the tissue homeostasis, the carcinogenesis, the bone mass, the metabolic profile, and the behavior [157].

Regarding the endocrine function, the gut microbiota regulates estrogens concentrations by secreting β-glucuronidase, an enzyme that deconjugates estrogens into their active forms. For this reason, intestinal dysbiosis can cause alteration of circulating estrogen levels [158]. In women, this dysregulation could be involved in the pathogenesis of several diseases such as obesity and metabolic syndrome, endometriosis, polycystic ovary syndrome, endometrial hyperplasia, cancer, and infertility [158]. In men, correlation studies between gut microbiota and infertility have not been performed; but it can be assumed that, by regulating estrogen levels, the microbiota can exert some influence on hypothalamic–pituitary feedback mechanisms.

Recently, Maretti noticed that three patients with idiopathic OAT who assumed an association of probiotic and prebiotic agents to treat intestinal disorders obtained an improvement in sperm quality/quantity [159]. So, he decided to carry out a pilot placebo-controlled study to evaluate the effect of this association on sperm parameters. Patients in the treatment group (n = 20) showed a statistically significant increase in the ejaculate volume, sperm concentration, progressive motility, and percentage of typical forms compared to placebo group (n = 21). Furthermore, an increase in FSH, LH and T levels and five spontaneous pregnancies occurred in the group of treated patients, while no pregnancies occurred in the placebo group [159]. The Authors hypothesized the following mechanism of action of probiotics plus prebiotics: influence on the hypothalamic kisspeptin production and consequent improvement in the pulsatile secretion of gonadotropins and T; optimization of the free radical concentration in the seminal fluid; regulation of the intestinal bacterial flora and subsequent improvement of the prostatic microenvironment [159]. If these preliminary data will be confirmed, this treatment could represent a new safe and inexpensive weapon in the fight against idiopathic male infertility, but further investigations are needed.

## 4. Conclusion

The medical therapies available for the empirical treatment of male idiopathic infertility are numerous. All the compounds, hormonal or non-hormonal, of which we have discussed, are potentially useful in the treatment of male infertility. However, the choice of the most appropriate treatment based on the clinical characteristics of each patient is necessary to avoid predictable therapeutic failures.

Among hormonal therapies, the compounds that have shown the greatest efficacy and, therefore, that are more frequently used in the clinical practice are FSH and SERMs [57]. The therapy needs, however, to be customized. For example, AIs, are indicated in patients with absolute or relative hyperestrogenism and with a low $T/E_2$ ratio, such as obese and metabolic patients [50]. SERMs are ineffective in men with altered hypothalamic-pituitary axis because of their inability to increase gonadotropin release after the removal of estrogen negative feedback on GnRH secretion [55]. FSH should not be given to patients with primary hypogonadism (indicated by FSH values ˃8 mIU/ml, and/or decreased inhibin B levels), and to patients for whom a therapeutic ineffectiveness can be expected [18]. These latter are the patients with TN/TN polymorphisms in exon 10 of FSHR gene, and with TT polymorphisms in position −211 of FSHB gene [30]. Conversely, FSH therapy could be particularly indicated in patients with high fragmented sperm DNA for its proven ability to decrease sperm DNA fragmentation rate [21] (Figure 2).

As for non-hormonal therapy, there is evidence that some substances with antioxidant and prokinetic properties are effective in improving sperm parameters [77,83]. These substances are often associated with each other in the products usually available on the market, and this makes it impossible to distinguish the effect of one from the other. The compounds with the strongest evidence of effectiveness are carnitines, CoQ10 and myoinositol [76,99,108]. A promising molecule could be lycopene [141].

Non-hormonal therapy can also be used in association with the hormonal therapy, of which it would seem to implement the beneficial effects. This has been shown especially for the association between SERMs and antioxidants [65].

A new and interesting field of intervention could be the regulation of the intestinal microbiota. Gut microbiota could, in some way, influence the male reproductive function [159]. However, no pathophysiological studies are available on this topic.

## 5. Expert opinion

We currently use the term ‘idiopathic’ to define every medical condition that we can not explain. In the field of male infertility, what we can not explain depends on how complete our diagnostic process has been. The limitation of many studies presented in this review is that the patients selection is heterogeneous and, in some cases, include patients in whom a more careful diagnostic work-up could have identified a cause (or a contributory cause) of the infertility. The identification of a suspected (or contributory) cause would allow to set up a targeted therapy and to reserve empirical therapy to

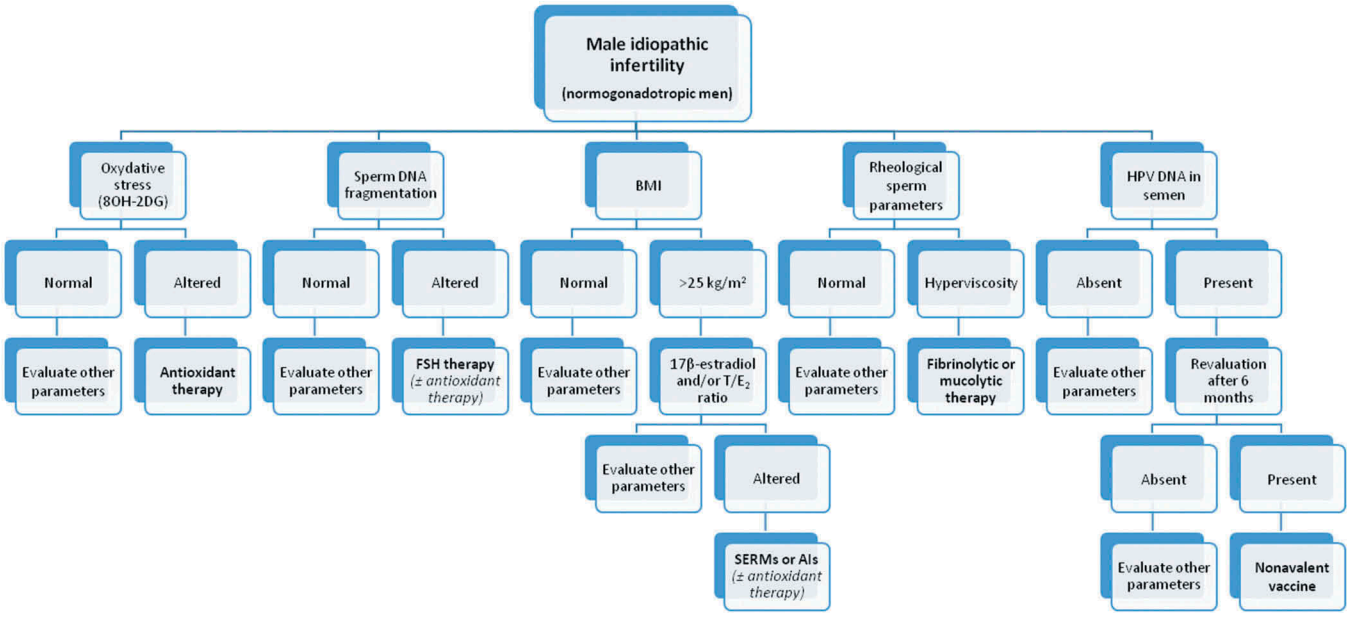


Figure 2. Diagnostic-therapeutic algorithm of the patient with male idiopathic infertility (normal gonadotropins levels and absence of female infertility factor).

a smaller number of cases. It would also avoid a certain number of therapeutic failures and allow to obtain cleaner and more homogeneous case series in clinical trials.

For example, alterations of seminal fluid rheological parameters—even in the absence of leukocytospermia—could decrease pregnancy rate per se. Seminal hyperviscosity may be caused by an hypofunction of male accessory glands due to inflammatory processes, to oxidative stress and/or to genetic factors [160]. In these cases, a fibrinolytic (e.g. serratiopeptidase, bromelain, escin) or mucolytic therapy (e.g. N-acetyl-cysteine), associated or not with antioxidants, can allow to achieve the goal of pregnancy [77].

Another pathological condition of the male genital tract often underdiagnosed but potentially treatable is human papillomavirus (HPV) infection. HPV infection is the most frequent sexually transmitted disease. It is mostly asymptomatic but it can cause alterations of sperm parameters (e.g. decreased motility and normal forms percentage), recurrent early miscarriages, and worse outcomes in ART [161,162]. Identification of HPV infection is important because vaccination can accelerate viral clearance and improve reproductive outcome [163]. Therefore, we suggest vaccination, preferably with the nonavalent formulation, if viral clearance does not occur spontaneously within 6 months. Moreover, in the case of ART, it is advisable to pre-treat the ejaculate with heparinase III, a substance capable of removing the virus from the surface of the spermatozoa [164].

Based on the above, we propose a therapeutic algorithm to be applied in clinical practice (Figure 2).

We wish for the future that clinicians and researchers work more and more together to lower the portion of male infertility today defined as 'idiopathic'. Scientific research must investigate the pathophysiological mechanisms that underlie infertility; only in this way, new targeted therapies can be developed. For example, innovative knowledge could come from the study of the interaction between the intestinal microbiota and the hypothalamic-pituitary-gonadal axis. Clinicians, on the other hand, must engage in primary and secondary prevention of infertility, following up patients since adolescence. For this purpose, we recommend that the diagnostic work-up is always carried out with the utmost precision, using all the available methods to identify any risk factor and any hidden causes (or concause) of infertility.

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